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EXAMINER	
MEAH, MOHAMMAD Y	

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1652	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/650,591	AFEYAN ET AL.	
	Examiner	Art Unit	
	MD. YOUNUS MEAH	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *11/24/08*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-5,14-17,19-34 and 37-41* is/are pending in the application.

4a) Of the above claim(s) *3,28 and 29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,5,14-17,19-27,30-34 and 37-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED

Claims 1, 3-5, 14-17, 19-34, 37-41 are pending. With supplemental amendment of this application filed 10/28/08, applicants amended claims 1, 15 and canceled claim 18. Claims 3 and 28-29 remain withdrawn.

Claim Rejections

35 U.S.C 102

Rejection of claims 1, 4, 14, 19, 21-27, 30, 33-34, 37 under 35 U.S.C. 102(b) as being anticipated by Davis et al. (WO 00/64485) is withdrawn after amendment of claim 1.

CLAIM Rejection - 35 U.S.C 103a

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a)A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 4, 14, 19-21, 22-27, 30, 33-34, 37 and 38 remain rejected under 35 U.S.C. 103(a) by Davis et al. (WO 00/64485) in view of, Bhatia et al (Intl. J. Cancer 2000, 85, 571-57) and Whitcomb et al. (US PAT 6406846) as explained in the prior action and restated again below:

Davis et al. teach fusion proteins wherein enzymes (serine protease, chymotrypsin, matrix metaloprotease, etc) which catalyze degradation of a specific target are conjugated to binding partners wherein the binding partner is ligand binding domain or protein or peptide or an antibody (immunoglobulin, Fab, $F(ab)_2$ claim 27) to

the target with or without a linker and resulting conjugate has greater (catalytic or more than one) activity than the unconjugated molecule. The chimeric protein of Davis et al. bind to the target and antagonize/inhibit /degrade a wide variety of receptors and/or intermediary signaling molecules such as cytokines, EGF-like factors, etc. Davis et al. use the fusion protein as a pharmaceutical composition wherein the targeted enzyme is protease and use the pharmaceutical composition for autoimmune disease, infectious diseases , cancer, etc. Davis et al. chimeric protein is chemically cross-linked fusion protein not a cotranslation fusion protein encoded by a recombinant nucleic acid made by of respective genes.

Protein conjugates can be made either by chemical conjugation or by gene fusion methods (applicants specification page 2 lines 26-30, but gene fusion methods have some particular advantages (see last paragraph of column one of page 571 of Bhatia et al Intl. J. Cancer 2000, 85, 571-577). It is well known in the prior art how to make fusion proteins by translation of a chimeric gene fusion (such as references supplied in the amendment of 5/7/08 by the applicants and also Bhatia et al Intl. J. Cancer 2000, 85, 571-577). Bhatia et al teach antibody-targeted enzymes made by gene fusion method. Therefore, one knowledgeable in prior art is **motivated** to make the protein conjugate of Davis et al by gene fusion methodology as taught by Bhatia et al.

Whitcomb et al. (US PAT 4510251) teach mesotrypsin, a trypsin-like protease (page 10 1st paragraph) that is fairly stable to proteolytic cleavage and also teach that mesotrypsin rapidly degrades and inactivates zymogens and other polypeptides.

As such it would have been obvious to one of ordinary skill in the art to use mesotrypsin, a trypsin-like protease, that is fairly stable to proteolytic cleavage as taught by Whitcomb et al. and make the fusion protein of Davis et al. by the method Bhatia et al. and use the resulting adzyme to inactivate substrate polypeptides by catalyzing the proteolytic cleavage of the said substrate polypeptide.

Claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over Davis et al. (WO 00/64485), in view of Bhatia et al (Intl. J. Cancer 2000, 85, 571-57) and Whitcomb et al. (US PAT 6406846) as applied to claims 1, 4, 14, 19-21, 22-27, 30, 33-34, 37 and 38 above, and further in view of Dolinar et al. (*Food tecnol and biotech*. 2000, 38, 5-9).

Davis et al., Bhattia et al. and Whitcomb et al. are described above. However Davis et al do not teach purification of fusion protein comprising protease domain using a reversible protease inhibitor.

Use of protease inhibitor in protein purification is well known in prior art. Dolinar et al. teach MMTS (methyl methane-thiosulfonate), a reversible protease inhibitor in the purification and refolding of a cystine proteinase type protein (page 6, column 2 last parg.). Therefore, one knowledgeable in prior art is **motivated** to purify fusion proteins comprising enzymes (serine protease, chymotrypsin, etc) which catalyze degradation of a specific target to a binding partners wherein the binding partner is an antibody (immunoglobulin) by the method of Dolinar et al. using a protease inhibitor so that said fusion protein would not cleaved by the protease.

As such it would have been obvious to one of ordinary skill in the art to use mesotrypsin – a trypsin-like protease that is fairly stable to proteolytic cleavage as taught by Whitcomb et al. to make a fusion protein as taught by Davis et al. by the method Bhatia et al and purify the said fusion protein as taught by Dolinar et al. using a protease inhibitor.

Claims 15-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Davis et al. (WO 00/64485), in view of Bhatia et al (Intl. J. Cancer 2000, 85, 571-57) and Whitcomb et al. (US PAT 6406846) as applied to claims 1, 4, 14, 19-21, 22-27, 30, 33-34, 37 and 38 above, and further in view of Guo et al. (Biotech. and Bioeng. 2000, 70, 456-463).

Davis et al. teach fusion proteins wherein enzymes (serine protease, chymotrypsin, etc) which catalyze degradation of a specific target are conjugated to binding partners wherein the binding partner is an antibody (immunoglobulin) through **a linker but not** through Gly_4Ser type of linker. Bhattia et al. and Whitcomb et al. are described above.

Guo et al. teach fusion proteins wherein an enzyme (ASNase) is conjugated to an immunoglobulin or fragment thereof or antibody (scFV) by a linker polypeptide $(Gly_4Ser)_3$. Guo et al also teach the advantage of $(Gly_4Ser)_3$ as linker, such as serine enhance hydrophilicity and glycyl residues provide conformational flexibility (page 457, column 1, 2nd parg). Therefore, one knowledgeable in prior art is **motivated to make** fusion proteins comprising enzymes (serine protease, chymotrypsin, etc) which

catalyze degradation of a specific target conjugating through $(Gly_4Ser)_3$ type linker to a binding partners wherein the binding partner is an antibody (immunoglobulin) by the method Bhatia et al.

As such it would have been obvious to one of ordinary skill in the art to use mesotrypsin – a trypsin-like protease that is fairly stable to proteolytic cleavage as taught by Whitcomb et al. to make a fusion protein as taught by Davis et al. by the method Bhatia et al conjugated via a linker as taught by Guo et al. and use the resulting adzyme to inactivate substrate polypeptides by catalyzing the proteolytic cleavage of the said substrate polypeptide.

Applicants' argue that Davis et al. chimeric protein is chemically cross-linked protein conjugate and Davis et al. especially teach advantage of chemical cross-linking and therefore one will not motivate to use cotranslation gene fusion technique.

Applicants' arguments files on 10/ 28/08 have been fully considered, but they found unpersuasive. Bhatia et al (Intl. J. Cancer 2000, 85, 571-577, page 571, 3rd paragraph) provide motivation to make fusion protein by gene fusion method as it teaches the advantages of the recombinant fusion protein such as easier to make, one well defined product obtained, and higher purity product compare to chemical conjugation. Thus one of ordinary skill in the art would have been **motivated** at the time of invention to make protein conjugate comprising two protein partners of Davis et al by gene fusion methodology (as taught by Bhatia et al).. As explain above, the combination of Bhatia et al, Whitcomb et al. and Davis et al. renders claim 41 obvious because claim 41 is broader in scope than claim 1 with regard to the protease domain.

Applicants' argument against Guo et al, is considered but is not found persuasive. Guo et al provide motivation to use $(Gly_4Ser)_3$ as linker. Guo et al teach the advantage of $(Gly_4Ser)_3$ as linker, such as serine enhance hydrophilicity and glycyl residues provide conformational flexibility (page 457, column 1 2nd parg). Therefore, one knowledgeable in prior art is **motivated** to combine Davis et al and Whitcomb et al with Gao et al. as Davis et al itself teach to introduce linker group in between catalytic domain and targeting domain and Guo et al, taught how to produce a protein (ASNase) conjugated to immunoglobulin (scFV) by a linker polypeptide $(Gly_4Ser)_3$. One knowledgeable in prior art can make a fusion protein by using chimeric gene comprising mesotrypsin domain, linker group and targeting domain.

.*Double Patenting Rejection*

Rejection of Claims 1, 4-5,14-17, 19-27,30-34, 37-41 provisionally under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 4-25 and 30-41 of copending Application No.10/792498 is maintained.

Rejection of claims 1, 4-5,14-17, 19-27,30-34, 37-41 provisionally under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 4-38, 40-46, 52-60, 66-104, 107-134 of copending Application No.10/650,592 is maintained.

Examiner agrees with applicant that the provisional Double patenting rejections may be withdrawn when all claims are otherwise allowable if the copending application is not allowed (however see MPEP 804 I(B)(1) for situations where this may not be the

case or when applicant submit terminal disclaimer, however until one of these conditions apply the rejections will be maintained.

Allowable Subject Matter/Conclusion

None of the claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mohammad Meah whose telephone number is 571-272-1261. The examiner can normally be reached on 8:30-5PM.
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, NASHAAT T NASHED can be reached on 571-272-0934. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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